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AWARD NUMBER: DAMD17-02-2-0018

TITLE: Topical Treatment of Cutaneous Leishmaniasis W/WR279396 Phase II Study

PRINCIPAL INVESTIGATOR: Pierre Buffet, M.D.

CONTRACTING ORGANIZATION: Centre de Recherche Clinique de Instiutut
75724 Paris Cedex 15 France

REPORT DATE: July 2006

TYPE OF REPORT: Final Addendum

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-07-2006	Final Addendum	1 Dec 2004 – 31 Mar 2006

4. TITLE AND SUBTITLE

Topical Treatment of Cutaneous Leishmaniasis W/WR279396 Phase II Study

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-02-2-0018

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Pierre Buffet, M.D.

E-Mail: pabuffet@pasteur.fr

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Centre de Recherche Clinique de Instiutut
75724 Paris Cedex 15 France

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

In the previous GCP phase 2 clinical study (HSRRB Log# A-9768.1) using investigational drug WR279396, cure rate was found to be 95.8% when evaluated at D50 with no relapse at D180 against L. major Old World Cutaneous Leishmaniasis (CL). During this reporting period, a second phase 2 clinical study was conceived, written, and initiated (HSRRB Log# A-9768.2 entitled "Topical Treatment of Old World Cutaneous Leishmaniasis with WR279396: Efficacy and tolerance of a regimen using an occlusive polyurethane dressing") that started in January 2006 at the Tunisia site to determine: (a) whether WR279396 when applied under a polyurethane occlusive bandage (Tegaderm™) is more efficient than application of the drug without occlusion; and (b) would administration of WR279396 once-a-day for 20 days be as effective as application twice-a-day for 20 days when compared to the results from study A-9768.1.

15. SUBJECT TERMS
No subject terms provided.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	17	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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INTRODUCTION

Analysis of the data from the previous clinical study with WR279396 that was completed in 2004 (HSRRB Log # A-9768.1) indicated that by day 50, complete cure rate was 95.8% in the treatment group and 75% in the placebo control group. Cure rate under placebo is this trial (75%) was higher than the cure rate under placebo (32%) in a previous trial performed in the same area using the same evaluation criterion (Ben Salah 95). The occlusive dressing (Tegaderm™) used during the ongoing trial may have positively influenced cure rate.

Thus, one of the two main objectives of this Phase 2 study is to determine whether WR279396 with occlusion (a polyurethane dressing) is more effective than WR279396 without occlusion.

The second objective is to determine if the administration of WR279396 once-a-day for 20 days is as effective as twice a day for 20 days when compared to the results from study A-9768.1. Simplification of the treatment and reduction of the number of adverse events (AEs) do to the removal of the Tegaderm™ from the patient skin twice a day is vital to the product.

Extensive objective and subjective local tolerance data will also be captured during this trial, as well as surrogate markers (parasite loads and aminoglycosides concentration in the deep dermis) that may also help to determine the optimal number and duration of treatments.

PURPOSE

This study is designed to answer two primary questions: (a) is occlusion necessary and useful, and (b) would administration of WR279396 once-a-day for 20 days be as effective as twice a day for 20 days when compared to the results from study A-9768.1. The answers to these questions will help define the design of a pivotal Phase 3 study to support regulatory approval of this drug.

STUDY INVESTIGATORS

Afif Ben Salah, MD, PhD is the study PI

SCIENTIFIC EXPERTS AND CONSULTANTS

Pierre Buffet, MD, PhD
Max Grögl, PhD

INSTITUTION(S)

Institute Pasteur
13 Place Pasteur BP, 74 Belvedere 1002
Tunis, Tunisia

SUBJECT POPULATION

The target study population are male and female patients in Tunisia, 15 to 75 years old, who are clinically suspected to have cutaneous leishmaniasis obtained in a region of the Old World.

TABLE 1: Subject Demographics For Protocol Log No. A-9768.2 Through 30 March 2005

Subject No.	Age	Gender
001	21	Female
002	47	Female
003	20	Female
004	38	Male
005	15	Male
006	16	Female
007	15	Female
008	17	Female
009	20	Male
010	50	Male
011	16	Female
012	17	Male
013	15	Female
014	16	Male
015	57	Female
016	42	Male
017	38	Male
018	19	Female
019	53	Male
020	75	Female
021	75	Male
022	17	Female
023	40	Female
024	40	Female
025	38	Male

TABLE 2. Total Number Of Subjects

Overall planned for study:	40
Site:	Tunisia:
Screened:	46
Enrolled in study:	25
By Group:	
Occlusion:	14
Non occlusion:	11
Dropped for any reason:	1

*One subject requested to be removed from the protocol and was treated with glucantime.

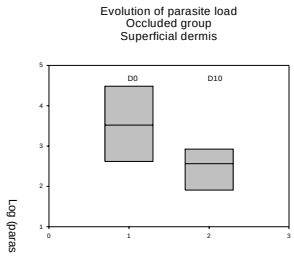
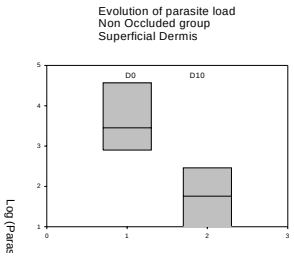
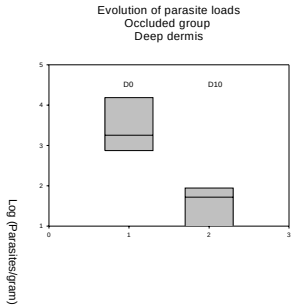
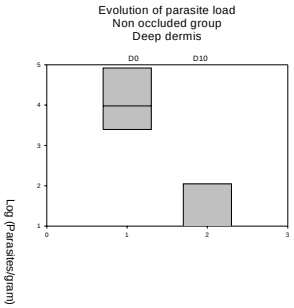
STUDY STATUS

This study initiated in January 2006. To date, 30 March 2005, twenty-five volunteers have been included, 14 in the occluded group and 11 in the non-occluded group. One patient has withdrawn from the study.

STUDY RESULTS

Preliminary data: A preliminary analysis of the results from 25 patient biopsies tested shows a decrease of the mean parasite load (superficial and deep dermis, occluded and non-occluded) from 3.69 log units at D0 to 1.59 log units at D10.

Figure 1 (shown on next page) shows the occlusion effect and lesion depth analysis. The decrease of parasite load is significant in all groups (i.e., occluded superficial and deep, non-occluded superficial and deep). There is a trend toward a more important decrease in the deep dermis as compared to superficial dermis. There is also a trend toward a greater decrease in the non occluded group.

	Occluded	Non occluded
Superficial		
Deep		

ADVERSE EXPERIENCES

There were no systemic toxicities or laboratory abnormalities found.

Eight patients had local reactions of short duration, all were Grade 1 (7 in the group occluded and 1 in the group non-occluded group).

SUBJECT DROPOUTS IN ASSOCIATION WITH ADVERSE EVENTS

There were no subjects withdrawn in association with adverse events. One subject withdrew his consent and was treated with Intralesional-Glucantime.

DEATHS

There were no deaths.

CONCLUSION

There are no conclusions. This study is still in progress.

ATTACHMENTS 1 AND 2 CONTINUED ON THE FOLLOWING PAGES:

ATTACHMENT 1:

Trip Report by Dr. Pierre Buffet, Institut Pasteur Paris, To Tunisia 09 – 12 December 2005

Trip Report Pierre Buffet Institut Pasteur Paris
Tunisia 09 – 12 December 2005

PROTOCOL: Topical Treatment of Old World Cutaneous Leishmaniasis with WR279396 (paromomycin/gentamicin ointment): Efficacy and tolerance of a regimen using an occlusive polyurethane dressing. IND 50 098. HSRRB Study Log Number A-9768.2

TRIP OBJECTIVES:

1. Bring supplies faster than usual process
    a. Multichanel pipetors
    b. Electric grinder
    c. Camera lenses, flash, batteries and plugs
    d. Tegaderm and lidocain cream
    e. Small plastics for cream mixing

2. Local team training with the help of Pr. Ben Salah and Pr. Hechmi Louzir on the following actions
    a. Take photographs
    b. Lesion measurements
    c. Perform biopsies
    d. Prepare and store samples for aminoglycosides dermal concentration
    e. Perform limiting dilution and capture data
    f. Upgrade corresponding SOPs when required

3. Check on status of funds transfer to Health Authorities in Sidi-Bouzid (facility rental)

DAILY ITINERARY:

Friday 2005-12-09

14:00 – 14:30	Home – Paris CDG Airport
16:20 – 20:00	CDG Airport – Tunis Carthage Airport
20:00 – 20:30	Tunis Carthage Airport– Hôtel Les Ambassadeurs
22:00 – 22:30	Meeting with Dr. Ben Salah Supplies given to Dr. Ben Salah : ❖ Multichanel pipetors ❖ Electric grinder ❖ Camera lenses, flash, batteries and plugs ❖ Tegaderm and lidocain cream ❖ Small plastics for cream mixing
22:30 – 24:00	Trip report, check last version of protocol and SOPs

Saturday 2005-12-10

9:00 – 11:45 Les Ambassadeurs Hotel Tunis – La Khasba Hotel Kairouan
Institut Pasteur in Tunis car and driver

17:00–20:00 Meeting with Dr. Hechmi Louzir

Check agreement on general structure of SOP 10, 11 and 12 provided in July.

Sunday 2005-12-11

9:00 – 10:00 Travel La Khasba Hotel – El Mnara site, Institut Pasteur in Tunis car and driver

10:00 – 11:20 El Mnara site.

- Check material and procedure for biopsy with Pr. Hechmi Louzir and Amor Zaatour.
- See 3 patients with suspected cutaneous leishmaniasis
- 25 yo male with one ulcerated nodule of the left foot. Biopsy justified for diagnosis, to be performed at the Sidi-Bouzid site.
- 19 yo female with one ulcer and regional edema. Antibiotic prescription and local antiseptic treatment by Mr. Farhat Mighri responsible of the Health center.
- 2 yo female with large ulceration of the left cheek, who would greatly benefit from compassionate application of WR279396.
- Training of Dr. Ben Salah for use of the new camera.

13:00 –16:30 Sidi Bouzid site.

- Check for heavy materiel availability. Certified hood in place (certification must be signed).
- Refrigerated incubator in place and operational with permanent temperature follow-up.
- Quality controls of refrigerators (including twice-a-day control of “drug” refrigerator) are OK.
- Biopsy and limiting dilution training in real condition from biopsy performed on patient 1 see above. Plates will be read by Amor Zaâtour next week.
- Dry runs on lesion measurement and photographs with Dr. Nathalie Messaoud and Dr. Hedi Afi. Reading of SOPs. Clarification on dressing used for non-occluded group (SOP clarified accordingly, signed by PI). Clarification provided on application of occluded dressing a few hours prior to lesion evaluation at D50 in order to help crust removal (no need to modify SOP). Clarification provided on induration measurement and capture.

17:00 – 21:00 Travel, Sidi-Bouzid – Tunis Les Ambassadeurs Hotel,
Institut Pasteur in Tunis car and driver

During trip, perform step by step analysis of the process with Mr. Amor Zaâtour and Dr. Ben Salah. Prepare list of optimizations to be introduced in SOPs 10 – 12. Provide clarification of reading steps. Clarification on positive and negative quality controls (see SOP #10).

Monday 2005-13-11	Les Ambassadeurs Hotel
9:00 – 13:00	Rewrite SOPs 10-12 under one SOP #10. Write Annex (Biopsy form).
14:00 – 16:00	Read carefully new SOP#10 with Mr. Amor Zaâtour and Dr. Ben Salah. Introduce last corrections.
16:00 – 16:50	Print SOP #12 including "Biopsy form" (Annex). Signed by PI who will add user's signature (Amor Zaâtour, Mr. or Mrs. X). Print short "training report". Signed by Dr. Ben Salah and P Buffet. Dr. Ben Salah will obtain signatures from other attendees and put the documents in file.

LISTEN TO PI'S PROGRAM :

(i) recruit potential volunteers at El Mnara and Sidi Bouzid sites
(ii) obtain lacking materiel (see check list below)
(iii) include patients.

Take list of needed items to be purchased in France.

16:50 – 17:20	Meeting with Dr. Hechmi Louzir. Check SOP #10.
17:30 – 18:10	Institut Pasteur Tunis – Tunis Carthage Airport
19:40 – 22:20	Tunis Carthage Airport – Paris CDG Airport Finish trip report. Write e-mails.

COMMENTS:

1. Additional training on at least two biopsies (human or not) before including the first patient would be useful.
2. Dr. Nathalie Ben Messaoud has to be trained again for biopsies before becoming responsible for this step i.e., it is advisable to have Pr. Mourad Mokni present for the first cohort.
3. To save time it would be useful to have someone assisting Mr. Amor Zaâtour with biopsy processing.
4. Lack of product for compassionate use (for selected but not included patients) may soon become a problem (community collaboration/Helsinky declaration compliance art #19).

ANNEXES:

1. Check list 1: Urgently needed items
    a. Xylocaine with adrenaline
    b. Safety needle and blade boxes
    c. Grinder fixation
    d. Grinder blade fixation
    e. Back-up grinder blade (France)

f. 200 l sterile tips (France)
g. Tape so seal plates
h. Sterile flat-bottom 96-well plates
i. Inverted microscope with trail (France)
j. Cryomarkers

2. Check list 2: Pending actions
    a. Reading plates from first training using Biopsy form (AZ)
    b. Obtain technician signature for hood certification (ABS)
    c. Use the new grinder full speed and check for culture (AZ/HL)
    d. Purchase materiel (GMo/ABS)
    e. Define date for second training/first inclusions (ABS)
    f. Ask on which account money should be transferred from Paris to Regional Health Center (groundplace for kids) (ABS)
    g. Report and check needed items list with MGr and PS (PB/GMo/ABS)
    h. Translate SOP#10 in French (GMo/ABS)

3. SOP # 10

Cooperative Agreement DAMD17-02-2-0018

ATTACHMENT 2

Trip Report by Dr. Gloria Morizot, Institut Pasteur Paris, To Tunisia 19 –24 February 2006

Trip Report by Dr. Gloria Morizot, Institut Pasteur Paris, To Tunisia 19 –24 February 2006

Protocol: Topical Treatment of Old World Cutaneous Leishmaniasis with WR279396 (paromomycin/gentamicin ointment): Efficacy and tolerance of a regimen using an occlusive polyurethane dressing. IND 50 098

TRAVELERS:

Afif BEN SALAH
Principal Investigator

Shirley ROACH
Monitor

Gloria MORIZOT
Study Logistic Coordinator

Subinvestigators:
Nathalie Messaoud
Amor Zaâtour
Abdelkarim El Fahem
Nabil Haj Hmida

OBJECTIVE

To collaborate with the monitoring visit

SUNDAY 19/02/06

13:30 Home – Paris CDG Airport
16:20 CDG Airport – Tunis Carthage Airport
19:00 Tunis Carthage Airport– Hôtel Les Ambassadeurs
20:00 Meeting with Dr. Ben Salah and Mrs Roach

Supplies given to Dr. Ben Salah:

a. Material of small surgery
b. Lidocain cream
c. Betametasona cream

MONDAY 20/02/06

09:00 Visit of the PI's office and epidemiologic office at IP Tunis.

09:00 Meeting with Pr. Abdeladhim Ben Abdeladhim (Director of Institut Pasteur of Tunis), Dr. Hechmi Louzir, Dr. Mokni Mourad, Dr. Ben Salah and Mrs Roach: Study presentation, objectives of monitoring.

13:30 Meeting with Mrs Roach discussion of the study documents
14:30 Les Ambassadeurs Hotel Tunis – La Khasba Hotel Kairouan
(IP Tunis car and driver)

TUESDAY 21/02/06

9:00 La Khasba Hotel – Elmnara site
10:00 Monitoring in Elmnara site (nurse: Mighri Farhat):
Following of screening and inclusion of patients
Monitoring of the consent process, clinical examination, audiogram drug application and filling CRF.
16:30 Visit of the Ouled Haffouz Center of Health (Centre de Santé de Base-CSB):
Screening of patient.
1800 Visit of the Sidi Bouzid site.
Debriefing of the day

WEDNESDAY 22/02/06

8:00 La Khasba Hotel – Sidi Bouzid site

Monitoring in the Sidi Bouzid site.
Checking of the Study File
Checking of CRFs
Monitor's queries and recommendations (proposal of the modifications in the protocol, ICF)
Debriefing of the day

THURSDAY 23/02/06

8:00 La Khasba Hotel – Sidi Bouzid site

Following of Biopsy process and downstream
Modifications in SSPs and Drug Accountability Form
Checking of the remaining CRFs
PI's answers to queries
17:00 Visit to the patient.

FRIDAY 24/02/06

09:00 Meeting with Dr Ben Salah, Mrs Roach and discussion of the Maj. Smith's E-mail

10:30 Meeting with Pr. Samir BOUBAKER (Tunis IRB chairman), Dr Ben Salah and Mrs Roach.

12:00 Institut Pasteur Tunis – Tunis Carthage Airport
16:00 Tunis Carthage Airport – Paris CDG Airport. Trip complete.